Claims 54-57, 59-61, 63, 65-66, 75, 77-78, 81, 85-86, 90, 92-93, 99, 103-104, 108, 110-111, 117, 119, 126-128, 215-217, and 219-220 have been amended to more particularly point out and distinctly claim Applicants' invention. New dependent claims 227-230 have been added. No new matter has been introduced.

Applicants respectfully request reconsideration of the claims rejections in view of the following arguments.

Claims 54-63, 65-68, 70-75, 77-80

Applicants respectfully submit that independent claim 54 is patentable over Anderson (US 6,168,948) because, for instance, Anderson does not disclose or suggest a lysing chamber containing at least one filter that captures the sample components as the sample flows through the lysing chamber. In Anderson, a textured wall 1906 has antibodies 1912 that bind to corresponding cell receptors within the sample. Thus, Anderson teaches a different method for cell capture. Anderson also does not disclose or suggest the step of forcing a volume of sample that is greater than the volume capacity of the lysing chamber to flow through the lysing chamber. These steps recited by Applicants in claim 54 provide important advantages. For example, Applicants' inclusion of a filter in the lysis chamber greatly cheapens and simplifies the method as compared to Anderson's reactive ion etching of protrusions 1908 that must then be functionalized with binding agents 1912. Moreover, Applicants' use of a filter in the lysing chamber and Applicants' forcing a sample volume that is greater than the volume capacity of the lysing chamber to flow through the lysing chamber provides for greater concentration of cells in the lysing chamber than would be possible using the method taught by Anderson. This concentration of cells in the lysing chamber is important for the detection of analyte, e.g., nucleic acid, that is present in a sample in very low starting copy number.

Applicants respectfully submit that independent claim 54 is patentable over Nelson (US 5,770,029) in view of Wilding (US 5,726,026 or 5,928,880) because, for instance, neither reference discloses or suggests a lysing chamber containing at least one filter that captures the sample components as the sample flows through the lysing

chamber. Applicants' use of a filter in the lysing chamber provides the advantages described above.

For at least the foregoing reasons, claim 54 and claims 55-63, 65-68, 70-75, 77-80 depending therefrom are patentable.

Claims 81-90, 92-98 and Claims 99-108, 110-116

Applicants respectfully submit that independent claims 81 and 99 are patentable over Anderson (US 6,168,948) in view of Nelson (US 5,770,029) because, for instance, Anderson does not disclose or suggest the step of forcing a volume of sample that is greater than the volume capacity of the lysing chamber to flow through the lysing chamber and into a waste chamber in the cartridge. Applicants' forcing a sample volume that is greater than the volume capacity of the lysing chamber to flow through the lysing chamber provides for greater concentration of cells in the lysing chamber. This concentration of cells in the lysing chamber is important for the detection of analyte, e.g., nucleic acid, that is present in a sample in very low starting copy number. Nelson does not cure the deficiencies of Anderson in failing to teach this method. In fact, as the Examiner points out, Nelson does not teach a lysing chamber at all.

Applicants respectfully submit that independent claims 81 and 99 are patentable over Nelson (US 5,770,029) in view of Wilding (US 5,726,026 or 5,928,880) because, for instance, neither reference discloses or suggests a lysing chamber containing solid phase material that captures the sample components as the sample flows through the lysing chamber. Applicants' use of solid phase material in the lysing chamber provides advantages, such as the concentration of cells in the lysing chamber which is important for the detection of analyte, e.g., nucleic acid, that is present in a sample in very low starting copy number.

For at least the foregoing reasons, claim 81 and claims 82-90, and 92-98 depending therefrom are patentable; and claim 99 and claims 100-108, 110-116 depending therefrom are patentable.

Claims 117-125, 126-137 and 227-228

Claims 117 and 126 have been amended to include the subject matter of claims 119 and 128, respectively, which the Examiner stated would be allowable. Applicants thank Examiner for the allowance. Dependent claims 118-125, 127-137, and 227-228 should also be allowable.

Claims 215-226 and 229-230

Applicants respectfully submit that independent claim 215 is patentable over Anderson (US 6,168,948) in view of Hansmann (US 5,707,799) and Mochida (US 5,147,607). First, it would not have been obvious to one skilled in the art to employ an array of structures as taught by Hansmann in the device of Anderson in an attempt to perform the method of claim 215. This is because there is no elution of analyte from the pillar structures of Hansmann. In fact, Hansmann's device does not even have an outlet port to make elution possible. Hansmann merely has a vent for venting gases from the device as it fills with sample. Nor would one skilled in the art be motivated to try to elute from the pillars of Hansmann, as the purpose of the device is to capture analyte on pillars coated with immobilized reagent and to detect the analyte on the pillars. Elution of the analyte would ruin the detection, and would be impossible because the device has no outlet port for elution of the analyte. Thus, it would not have been obvious for one skilled in the art to freely substitute a device with pillars as taught by Hansmann into Anderson.

Second, even if the proposed combination of Anderson and Hansmann were legally justified, which Applicants submit it is not, the proposed combination would be inoperable. If one skilled in the art tried to stick the chip with pillars device as taught by Hansmann into a chamber of the device taught by Anderson in an attempt to perform the method of claim 215, the combination would be inoperable since the Hansmann device lacks an outlet port that permits liquid flow out of the device. Hansmann's device is not "a flow-through chip" as required by claim 215.

Third, liquid does not come out of Hansmann's device, and therefore the proposed combination would still not allow step (c) of claim 215 "forcing the lysed sample to flow through the extraction chamber and out of the chip" or step (d) "forcing an

elution fluid to flow through the extraction chamber and out of the chip." Mochida does not cure the deficiencies of Hansmann in failing to teach flow of a lysed sample or elution fluid out of a chip.

Applicants respectfully submit that independent claim 215 is patentable over Nelson (US 5,770,029) in view of Wilding (US 5,726,026 or 5,928,880), Hansmann (US 5,707,799) and Mochida (US 5,147,607). First, it would not have been obvious to one skilled in the art to employ an array of structures as taught by Hansmann in the device of Nelson in an attempt to perform the method of claim 215. This is because there is no elution of analyte from the pillar structures of Hansmann. In fact, Hansmann's device does not even have an outlet port to make elution possible. Hansmann merely has a vent for venting gases from the device as it fills with sample. Nor would one skilled in the art be motivated to try to elute from the pillars of Hansmann, as the purpose of the device is to capture analyte on pillars coated with immobilized reagent and to detect the analyte on the pillars. Elution of the analyte would ruin the detection, and would be impossible because the device has no outlet port for elution of the analyte. Thus, it would not have been obvious for one skilled in the art to freely substitute a device with pillars as taught by Hansmann into the enrichment channel of Nelson.

Second, even if the proposed combination of Nelson and Hansmann were legally justified, which Applicants submit it is not, the proposed combination would be inoperable. If one skilled in the art tried to stick the chip with pillars device as taught by Hansmann into the enrichment channel 62 of the device 50 taught by Nelson (Fig. 4) in an attempt to perform the method of claim 215, the combination would be inoperable since the Hansmann device lacks an outlet port that permits liquid flow out of the device. Hansmann's device is not "a flow-through chip" as required by claim 215.

Third, liquid does not come out of Hansmann's device, and therefore the proposed combination would still not allow step (c) of claim 215 "forcing the lysed sample to flow through the extraction chamber and out of the chip" or step (d) "forcing an elution fluid to flow through the extraction chamber and out of the chip." Mochida does

not cure the deficiencies of Hansmann in failing to teach flow of a lysed sample or elution fluid out of a chip.

For at least the foregoing reasons, claim 215 and claims 216-226 and 229-230 depending therefrom are patentable.

Double-Patenting Rejections

Claims 54-56, 58-60, 62-82, 84-100, 102-118, 120-127, 129-136, and 215-226 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-22 and 103-107 of copending application no. 09/513,443 in view of Anderson et al. or Wilding et al. (USP 5,726,026 or 5,928,890).

Claims 54-56, 58-60, 62-70, 73-82, 84-96, 99-100, 102-114, 117, 118, 120-124, 126, 127, and 129-134 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of copending application no.09/800,590) in view of Nelson et al. and Wilding or Anderson et al.

Applicants defer the filing of a terminal disclaimer in response to these rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 650-326-2400.

Respectfully submitted,

Chun-Pok Leung
Reg. No. 41,405

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834

Tel: 650-326-2400
Fax: 415-576-0300
RL:rl
PA 3303559 v1

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claims 54-57, 59-61, 63, 65-66, 75, 77-78, 81, 85-86, 90, 92-93, 99, 103-104, 108, 110-111, 117, 119, 126-128, 215-217, and 219-220; and add new dependent claims 227-230 as follows. Please cancel without prejudice non-elected species of claims 137-214 for which Applicants will file a divisional application. Please also cancel claims 64, 69, 76, 91, and 109.

54. (amended) A method for extracting an analyte from a fluid sample, the method comprising the steps of:

a) introducing the sample into a cartridge having:

i) a lysing **[region]** **chamber** for lysing sample components to release the analyte therefrom, wherein the lysing **[region]** **chamber** contains **[solid phase material]** **at least one filter** for capturing the sample components as the sample flows through the lysing **[region]** **chamber**; and

ii) an analyte capture region containing capture material for capturing the analyte;

b) forcing the sample to flow through the lysing **[region]** **chamber** to capture the sample components with the **[solid phase material]** **filter, wherein the volume of sample forced to flow through the lysing chamber is greater than the volume capacity of the lysing chamber**;

c) lysing the sample components in the lysing **[region]** **chamber** to produce a lysate containing the analyte;

d) forcing the lysate to flow through the capture region, thereby capturing the analyte with the capture material; and

e) eluting the analyte from the capture region.

55. (amended) The method of claim 54, wherein the cartridge further includes a reaction chamber, and the method further comprises the steps of:

i) forcing the eluted analyte to flow into the reaction chamber;

ii) **[chemically]** reacting the analyte in the reaction chamber; and

iii) detecting a reaction product.

56. (amended) The method of claim 55, wherein the analyte comprises nucleic acid, and wherein the steps of **[chemically]** reacting the analyte and detecting the reaction product comprise amplifying the nucleic acid and detecting the amplified nucleic acid.

57. (amended) The method of claim 55, wherein the chemical reaction requires temperature control of the reaction chamber, the portion of the cartridge defining the reaction chamber protrudes from the rest of the cartridge body, and the method further comprises the steps of inserting the reaction chamber into a thermal sleeve and heating or cooling the reaction chamber according to a time/temperature profile.

59. (amended) The method of claim 54, further comprising the steps of:

i) forcing the eluted analyte to flow into a reaction vessel coupled to the cartridge;

ii) **[chemically]** reacting the analyte in the reaction vessel; and

iii) detecting a reaction product.

60. (amended) The method of claim 59, wherein the analyte comprises nucleic acid, and wherein the steps of **[chemically]** reacting the analyte and detecting the

reaction product comprise amplifying the nucleic acid and detecting the amplified nucleic acid.

61. (amended) The method of claim 59, wherein the **[chemical]** reaction requires temperature control of the reaction vessel, and the method further comprises the steps of inserting the vessel into a thermal sleeve and heating or cooling the vessel according to a time/temperature profile.

63. (amended) The method of claim 54, wherein the step of lysing the sample components comprises transferring ultrasonic energy to the lysing **[region]** **chamber** using an ultrasonic transducer coupled to a wall of the lysing **[region]** **chamber**.

65. (amended) The method of claim **[64]** **63**, wherein the step of lysing the sample components further comprises agitating particles or beads in the lysing chamber to rupture the sample components.

66. (amended) The method of claim 63, further comprising the step of placing a lysis buffer in the lysing **[region]** **chamber**, the lysis buffer containing a lysing reagent.

75. (amended) The method of claim 54, wherein the analyte is eluted from the capture region by forcing elution fluid to flow through the capture region, and wherein the volume of sample forced to flow through the lysing **[region]** **chamber** is greater than the volume of elution fluid forced to flow through the capture region, whereby the analyte extracted from the sample is concentrated in the smaller volume of elution fluid.

77. (amended) The method of claim **[76] 54**, wherein the ratio of the volume of sample forced to flow through the lysing chamber to the volume capacity of the lysing chamber is at least 2:1.

78. (amended) The method of claim 54, wherein the volume of sample forced to flow through the lysing **[region] chamber** is at least 1 ml.

81. (amended) A method for extracting nucleic acid from a fluid sample and for amplifying the nucleic acid, the method comprising the steps of:

a) introducing the sample into a cartridge having:

i) a lysing **[region] chamber** for lysing sample components to release the nucleic acid therefrom, **wherein the lysing chamber contains solid phase material for capturing the sample components as the sample flows through the lysing chamber**;

ii) a capture region, the capture region comprising a channel or chamber containing capture material for capturing the nucleic acid;

iii) at least one waste chamber; and

iv) a reaction chamber for amplifying the nucleic acid;

b) forcing the sample to flow through the lysing chamber and into the at least one waste chamber to capture the sample components with the solid phase material, wherein the volume of sample forced to flow through the lysing chamber is greater than the volume capacity of the lysing chamber;

[b] c) lysing the sample components in the lysing **[region] chamber** to produce a lysate containing the nucleic acid;

[c] d) forcing the lysate to flow through the capture region, thereby capturing the nucleic acid with the capture material;

[d] **e)** forcing the lysate that has flowed through the capture region to flow into the waste chamber;

[e] **f)** forcing an elution fluid to flow through the capture region to elute the captured nucleic acid from the capture region;

[f] **g)** forcing the eluted nucleic acid to flow into the reaction chamber; and

[g] **h)** amplifying the nucleic acid in the reaction chamber.

85. (amended) The method of claim 81, wherein **[the lysing region comprises a lysing chamber containing solid phase material for capturing the sample components, and the method further comprises the step of forcing the sample to flow through the lysing chamber and into the at least one waste chamber, thereby capturing the sample components with the solid phase material in the lysing chamber]** **the lysate is forced to recirculate through the capture region prior to being forced to flow into the waste chamber**.

86. (amended) The method of claim **[85]** **81**, wherein the step of lysing the sample components comprises transferring ultrasonic energy to the lysing chamber using an ultrasonic transducer coupled to a wall of the lysing chamber.

90. (amended) The method of claim **[85]** **81**, wherein the volume of sample forced to flow through the lysing chamber is greater than the volume of elution fluid forced to flow through the capture region, whereby the nucleic acid extracted from the sample is concentrated in the smaller volume of elution fluid.

92. (amended) The method of claim **[85]** **81**, wherein the ratio of the volume of sample forced to flow through the lysing chamber to the volume capacity of the

lysing chamber is at least 2:1.

93. (amended) The method of claim **[85]** **81**, wherein the volume of sample forced to flow through the lysing chamber is at least 1 ml.

99. (amended) A method for separating nucleic acid from a fluid sample and for amplifying the nucleic acid, the method comprising the steps of:

a) introducing the sample into a cartridge having:

i) a lysing **[region]** **chamber** for lysing sample components to release the nucleic acid therefrom, **wherein the lysing chamber contains solid phase material for capturing the sample components as the sample flows through the lysing chamber**;

ii) a capture region comprising a channel or chamber containing capture material for capturing the nucleic acid; and

iii) at least one waste chamber;

b) forcing the sample to flow through the lysing chamber and into the at least one waste chamber to capture the sample components with the solid phase material, wherein the volume of sample forced to flow through the lysing chamber is greater than the volume capacity of the lysing chamber;

[b] **c)** lysing the sample components in the lysing **[region]** **chamber** to produce a lysate containing the nucleic acid;

[c] **d)** forcing the lysate to flow through the capture region, thereby capturing the nucleic acid with the capture material in the capture region;

[d] **e)** forcing the lysate that has flowed through the capture region to flow into the waste chamber;

[e] **f)** forcing an elution fluid to flow through the capture region to elute the captured nucleic acid from the capture region;

[f] **g)** forcing the eluted nucleic acid to flow into a reaction vessel coupled to the cartridge; and

[g] **h)** amplifying the nucleic acid in the reaction vessel.

103. (amended) The method of claim 99, wherein **[the lysing region comprises a lysing chamber containing solid phase material for capturing the sample components, and the method further comprises the step of forcing the sample to flow through the lysing chamber and into the at least one waste chamber, thereby capturing the sample components with the solid phase material in the lysing chamber]** **the lysate is forced to recirculate through the capture region prior to being forced to flow into the waste chamber**.

104. (amended) The method of claim **[103]** **99**, wherein the step of lysing the sample components comprises transferring ultrasonic energy to the lysing chamber using an ultrasonic transducer coupled to a wall of the lysing chamber.

108. (amended) The method of claim **[103]** **99**, wherein the volume of sample forced to flow through the lysing chamber is greater than the volume of elution fluid forced to flow through the capture region, whereby the nucleic acid extracted from the sample is concentrated in the smaller volume of elution fluid.

110. (amended) The method of claim **[103]** **99**, wherein the ratio of the volume of sample forced to flow through the lysing chamber to the volume capacity of the lysing chamber is at least 2:1.

111. (amended) The method of claim **[103]** **99**, wherein the volume of sample forced to flow through the lysing chamber is at least 1 ml.

117. (amended) A method for **[separating]** **extracting** nucleic acid from a fluid sample and for amplifying the nucleic acid, the method comprising the steps of:

a) introducing the sample into a cartridge having:

i) a capture region, the capture region comprising a channel or chamber containing capture material for capturing the nucleic acid; and

ii) a waste chamber for receiving waste fluid from the capture region;

b) forcing the sample to flow through the capture region, thereby extracting the nucleic acid from the sample with the capture material in the capture region;

c) forcing the remaining sample fluid that has flowed through the capture region to flow into the waste chamber;

d) forcing an elution fluid to flow through the capture region to elute the captured nucleic acid from the capture region;

e) forcing the eluted nucleic acid to flow into a reaction vessel coupled to the cartridge; and

f) amplifying the nucleic acid in the reaction vessel, **wherein the temperature of the reaction vessel is controlled by inserting the vessel into a thermal sleeve and heating or cooling the vessel according to a time/temperature profile**.

119. (amended) The method of claim 117, wherein **[the temperature of the reaction vessel is controlled by inserting the vessel into a thermal sleeve and heating or cooling the vessel according to a predetermined time/temperature profile]** **the sample is forced to recirculate through the capture region prior to being forced to flow into the waste chamber**.

126. (amended) A method for **[separating]** **extracting** nucleic acid from a fluid sample and for amplifying the nucleic acid, the method comprising the steps of:

a) introducing the sample into a cartridge having:

i) a flow path through a capture region, the capture region comprising a channel or chamber containing capture material for capturing the nucleic acid;

ii) a waste chamber for receiving waste fluid from the capture region; and

iii) a reaction chamber for amplifying the nucleic acid;

b) forcing the sample to flow through the capture region, thereby capturing the nucleic acid with the capture material;

c) forcing the remaining sample fluid that has flowed through the capture region to flow into the waste chamber;

d) forcing an elution fluid to flow through the capture region to elute the captured nucleic acid from the capture region;

e) forcing the eluted nucleic acid to flow into the reaction chamber; and

f) amplifying the nucleic acid in the reaction chamber, **wherein the temperature of the reaction chamber is controlled by inserting the reaction chamber into a thermal sleeve and heating or cooling the reaction chamber according to a time/temperature profile**.

127. (amended) The method of claim 126, further comprising the step of detecting the amplified nucleic acid in the reaction **[vessel]** **chamber**.

128. (amended) The method of claim 126, wherein **[the portion of the cartridge defining the reaction chamber protrudes from the rest of the cartridge body,**

and wherein the temperature of the reaction chamber is controlled by inserting the reaction chamber into a thermal sleeve and heating or cooling the reaction chamber according to a time/temperature profile] **the sample is forced to recirculate through the capture region prior to being forced to flow into the waste chamber**.

215. (amended) A method for separating an analyte from a fluid sample, the method comprising the steps of:

a) introducing the sample into a cartridge having:

i) a lysing region for lysing sample components to release the analyte therefrom; and

ii) a flow-through **[microfluidic]** chip for capturing the analyte, the **[microfluidic]** chip comprising a body having an extraction chamber and an array of microstructures extending into the extraction chamber for capturing the analyte, wherein each of the microstructures has an aspect ratio (height to width) of at least 2:1;

b) lysing the sample components in the lysing region;

c) forcing the lysed sample to flow through the extraction chamber and out of the **[microfluidic]** chip, thereby capturing the analyte with the microstructures in the extraction chamber;

d) eluting the captured analyte from the **[microfluidic]** chip by forcing an elution fluid to flow through the extraction chamber and out of the **[microfluidic]** chip.

216. (amended) The method of claim 215, wherein the cartridge further includes a reaction chamber, and the method further comprises the steps of:

i) forcing the eluted analyte to flow into the reaction chamber;

ii) **[chemically]** reacting the analyte in the reaction chamber; and

iii) detecting a reaction product.

217. (amended) The method of claim 216, wherein the analyte comprises nucleic acid, and wherein the steps of **[chemically]** reacting the analyte and detecting the reaction product comprise amplifying the nucleic acid and detecting the amplified nucleic acid.

219. (amended) The method of claim 215, further comprising the steps of:

i) forcing the eluted analyte to flow into a reaction vessel coupled to the cartridge;

ii) **[chemically]** reacting the analyte in the reaction vessel; and

iii) detecting a reaction product.

220. (amended) The method of claim 219, wherein the analyte comprises nucleic acid, and wherein the steps of **[chemically]** reacting the analyte and detecting the reaction product comprise amplifying the nucleic acid and detecting the amplified nucleic acid.

--227. (new claim) The method of claim 117, further comprising the step of lysing the sample prior to forcing the lysed sample to flow through the capture region.

228. (new claim) The method of claim 126, further comprising the step of lysing the sample prior to forcing the lysed sample to flow through the capture region.

229. (new claim) The method of claim 216, wherein the reaction requires temperature control of the reaction chamber, and the method further comprises the steps of inserting the reaction chamber into a thermal sleeve and heating or cooling the reaction chamber according to a time/temperature profile.

230. (new claim) The method of claim 219, wherein the reaction requires temperature control of the reaction vessel, and the method further comprises the steps of inserting the vessel into a thermal sleeve and heating or cooling the vessel according to a time/temperature profile.--